Remarks

Claims 9, 11, 12, 14, 23-26, and 44-53 were pending. By this amendment, claims 23-26, 44-47, 49, 50, 52 and 53 are cancelled. No claims are added. Therefore, claims 9, 11, 12, 14, 48 and 51 are now pending.

Summary of Telephone Interview with Examiner

Applicants thank Examiner Whiteman for the courtesy of a telephone interview with Applicants' representative Sheree Lynn Rybak, Ph.D. on September 6, 2006. During this interview, the 35 U.S.C. § 103(a) rejections were discussed.

Examiner Whiteman was impressed by the Morishita *et al.* (*Hypertension* 44:203-9, 2004) article submitted with Dr. Morishita's July 8, 2006 declaration, showing that the claimed method works in human subjects.

The half-life of transgene expression was also discussed. Applicants presented several articles predating the filing date of the application, demonstrating that transgene expression is generally short-term, regardless of the gene. Applicants' representative explained that in view of these articles, one skilled in the art would expect that more frequent administration would be needed to provide a therapeutic effect (e.g. more than once every few weeks). Examiner Whiteman indicated that this evidence could be used to demonstrate that whether a transgene provides long-term expression cannot be predicted, and that the inventors' results appeared non-obvious. Applicants' representative agreed to submit copies of these articles with the response.

Elections/Restrictions

Claim 11 includes non-elected species (claims 24 and 45 are cancelled). However, it is Applicants position that generic claim 9 is now in condition for allowance, and request that the remaining species in claim 11 be searched.

35 U.S.C. § 103(a)

Claims 9, 11, 12, 14, 23-26, and 51-52 remain rejected under 35 U.S.C. § 103(a) as unpatentable over Isner *et al.* (WO 98/19712), an article from the Japan Financial Times (December 14, 1998), and Li *et al.*, (U.S. Patent No. 6,066,123) in further view of Morishita

et al. (EP 0847757). In addition, claims 44-47, 50 and 53 are rejected under 35 U.S.C. §103(a), as allegedly being unpatentable over Isner *et al.* (WO 98/19712) in combination with an article from the Japan Financial Times (December 14, 1998) in further view of Morishita *et al.* (EP 0847757). Applicants disagree and request reconsideration.

It is asserted on page 5 of the Office action that is would be obvious to a person of ordinary skill in the art to administer a nucleic acid encoding HGF once every few days or few weeks to treat lower limb ischemic disease. On page 7 of the Office action, it is stated that the features upon which Applicant relied (i.e. every few weeks) are not recited in the rejected claims. The claims have been amended to clarify that the administration of HGF is every few weeks. However, the administration form according to the present invention is not limited to HVJ-liposome.

At the time of the invention, those skilled in the art understood that transgene expression continues for at most two weeks after gene transfer, and that the greatest levels of expression are observed shortly after transfection (e.g. within 1-5 days). As a result, it was not expected that HGF expression would be sustained for a few weeks and a sufficient therapeutic effect would be obtained if only administered once over this time period. Evidence that those skilled in the art understood that transgene expression is transient is provided in several references available prior to the filing date of the present application (October 1999). For example:

(1) Thornton *et al.* (*Biochem. Biophys. Res. Commun.* 246:654-9, 1998) disclose that maximal expression of both the inducible nitric oxide synthase (iNOS) and chloramphenicol acetyl transferase (CAT) transgene occurred at 48 hours with a rapid decline after this time point (see Abstract). For example, expression of the CAT transgene was maximal at 2 days, then dropped precipitously between days 2 and 5, and remained low up to day 10, at which point very little expression was observed (see Results at page 656 and Figure 2).

(2) Denham *et al.* (*Ann. Surg.* 227(6):812-20, 1998) disclose that liposome-mediated transfer of a human IL-10 transgene is an effective method to transfect the

murine pancreas for up to 2 weeks (see page 817, column 1, second paragraph). However, the level of pancreatic human IL-10 mRNA expression was highest 1 day after transfection, with levels decreasing over 14 days (page 815, column 1, fourth full paragraph, and Figure 2 and its legend).

(3) Vogel (*Proc. Assoc. Am. Physicians* 111:190-7, May-Jun 1999) discloses that transgene expression from a plasmid is transient (see Abstract). Vogel observed that although expression of β-gal mRNA was initially high and easily detectable the first day following injection of the transgene, expression decline rapidly during the next 2-3 days. Vogel never observed long-term transgene expression (see page 192, column 2, lines 8-12 from the top and lines 6-4 from the bottom; also see Figure 2).

(4) Denham *et al.* (*J. Gastrointest. Surg.* 2(1):95-101, 1998) discloses that CAT transgene expression was maximal in pancreas, lungs, and liver at 12 hours following i.p. injection of the CAT transgene, with decreasing CAT activity over the ensuing 14 days (see Abstract; paragraph bridging pages 97 and 98; page 100, left column, last paragraph; page 100, right column, lines 24-26; and Fig. 2A-C).

(5) Kurata *et al.* (*J. Allergy Clin. Immunol.* 103:S471-84, May 1999) discloses in vivo expression of LacZ, luciferase, and GM-CSF transgenes using adenoviruses, and suggests that adenoviruses can be used to express cytokine transgenes for 2 weeks (see Abstract; and page S480, right column, second full paragraph). As shown in Fig. 2, β-gal activity resulting from expression of the LacZ trangene resulted in maximum expression on days 3-5 following transfection, and disappeared before day 14 (page S474, left column). As shown in Fig. 6B and 6D, luciferase activity resulting from expression of the luciferase transgene was similar on days 3 and 7 in the liver, and by day 14, was undetectable. As shown in Figs. 7A-B, expression of GM-CSF was not detectable by day 14.

Copies of the five cited references are provided in the IDS enclosed with this RCE application.

These teachings available before the priority date of the present application demonstrate that regardless of the transgene expressed, maximal expression is observed shortly after transfection (such as 1-5 days), and that by day 14, levels are virtually undetectable. Based on at least these five references, at the time of the invention it would be unexpected to one skilled in the art that therapeutic effects could be obtained by administration of a gene "once every few weeks" as presently claimed. As stated in paragraph 6 of Dr. Morishita's July 8, 2006 declaration (and Morishita *et al.*, *Hypertension* 44:203-9, 2004 submitted with the declaration), the inventors have demonstrated that administration of HGF gene once every few weeks (such as once every four weeks) is therapeutic for subjects having diabetic ischemic disease. That such infrequent administration would be therapeutic was not expected due to the short half-life of transgenes expected at the time of the invention discussed above. This unexpectedly superior result rebuts any allegation that the cited references establish a *prima facie* case of obviousness. Therefore, Applicants request that the 35 U.S.C. §103(a) rejection be withdrawn.

Claims 44-47, 50 and 53 are also rejected under 35 U.S.C. §103(a). As these claims are cancelled, the rejection is moot, and Applicants request that it be withdrawn.

If any minor issues remain to be resolved before a Notice of Allowance is issued, the Examiner is invited to telephone the undersigned.

Respectfully submitted,

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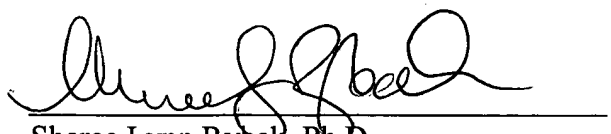
By 
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